Hypogammaglobulinemia after cardiopulmonary bypass in infants

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Background: Hypogammaglobulinemia has been reported after cardiac surgery and may be associated with adverse outcomes. We sought to define baseline immunoglobulin (Ig) concentration in neonates and infants with congenital heart disease, determine their course after cardiopulmonary bypass (CPB), and determine if post-CPB hypogammaglobulinemia was associated with increased morbidity.

Methods: This was a single-center, retrospective analysis of infants who underwent cardiac surgery with CPB between June 2010 and December 2011. The Ig concentration was obtained from banked plasma of 47 patients from a prior study (pre-CPB, immediately post-CPB, and 24 and 48 hours post-CPB). In addition, any Ig levels drawn for clinical purposes after CPB were included. Ig levels were excluded if drawn after chylothorax diagnosis or intravenous IgG administration.

Results: The median age was 7 days. Preoperative Ig concentration was similar to that described in healthy children. IgG level decreased to less than 50% of preoperative concentration by 24-hour post-CPB and failed to recover by 7 days. Of 47 patients, 25 (53%) had low IgG (<248 mg/dL) after CPB. Despite no difference in demographics or risk factors between patients with low and normal IgG, low IgG patients had more positive fluid balance at 24 hours and increased proinflammatory plasma cytokine levels, duration of mechanical ventilation, and cardiac intensive care unit length of stay. In addition, low IgG patients had an increased incidence of postoperative infections (40% vs 14%; $P = .056$).

Conclusions: Hypogammaglobulinemia occurs in half of infants after CPB. Its association with fluid overload and increased inflammatory cytokines suggests it may result from capillary leak. Postoperative hypogammaglobulinemia is associated with increased morbidity, including more secondary infections. (J Thorac Cardiovasc Surg 2014;147:1587-93)

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Postoperative hypogammaglobulinemia has been described in children and adults undergoing cardiac surgery with cardiopulmonary bypass (CPB). Potential causes may include hemodilution, destruction of immunoglobulin (Ig) by CPB, and extravasation into the interstitial space due to systemic inflammation and capillary leak syndrome.[1-3] Losses due to proteinuria and sequestration into the peritoneal and pleural spaces may contribute as well.[4,5] IgG is an integral component of the humoral immune system, and hypogammaglobulinemia has been associated with infectious risk in other populations.[6,7] Pre- and 24-hour post-CPB Ig concentrations in older children have been described,[8] but the incidence and clinical importance of post-CPB hypogammaglobulinemia in neonates and infants undergoing cardiac surgery with CPB are unknown.

We designed this study with the following aims: (1) to determine the normal preoperative range of IgG, IgM, and IgA in neonates with congenital heart disease; (2) to determine the impact of CPB on postoperative Ig concentrations; and (3) to determine whether hypogammaglobulinemia is associated with increased postoperative morbidity, including nosocomial infection. We hypothesized that hypogammaglobulinemia is common in neonates and infants after CPB and is associated with increased morbidity.

METHODS

Patients and Data Collection

This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. This is a retrospective study evaluating preoperative and postoperative plasma Ig concentrations (IgA, IgG, and IgM) in children undergoing complex cardiac surgery with CPB from June 1, 2010, to December 31, 2011, at our institution. Because of its retrospective design, informed consent was not required. Ig concentrations were acquired for inclusion via 2 methods: (1) analysis of banked plasma obtained from 47 consecutively enrolled subjects for a prior study that evaluated the impact of early postoperative peritoneal dialysis (PD) on neonates

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Abbreviations and Acronyms

AKI = acute kidney injury
BSI = bloodstream infection
CICU = cardiac intensive care unit
CPB = cardiopulmonary bypass
FFP = fresh frozen plasma
Ig = immunoglobulin
IVIG = intravenous immunoglobulin
OR = operating room
PD = peritoneal dialysis
POD = postoperative day
PRBC = packed red blood cell
SIRS = systemic inflammatory response syndrome
VAP = ventilator-associated pneumonia

and infants (4 potential time points per patient: pre-CPB, immediately post-CPB, and 24 and 48 hours post-CPB) and (2) review of the electronic records of the same 47 patients for postoperative Ig levels drawn for clinical purposes beyond 48 hours. Ig levels obtained after diagnosis of chylothorax, after treatment with intravenous immunoglobulin (IVIG), or while receiving extracorporeal membrane oxygenation were excluded from analysis. All other demographic, clinical, and laboratory data were obtained from our institutional clinical database. All laboratory values represent measurements on the day hypogammaglobulinemia was diagnosed, except where indicated.

Immunoglobulin and Cytokine Analysis

All plasma was stored at −80°C. All Ig concentrations were determined using the Fusion 5.1 analyzer (Ortho Clinical Diagnostics, Rochester, NY) in our institutional clinical laboratory. Interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor-α were assayed using a multiplex electrochemiluminescence detection method (MSD 2400 imager; Meso Scale Diagnostics, Gaitherburg, Md). Minimum sensitivities were 0.457 pg/mL for IL-1β, 0.018 pg/mL for IL-6, 0.10 pg/mL for IL-8, 0.809 pg/mL for IL-10, 0.780 pg/mL for IL-12, and 0.857 pg/mL for tumor necrosis factor-α.

Definitions

Because normal Ig concentrations for children with congenital heart disease have not previously been described, hypogammaglobulinemia for this study was defined as 2 SDs lower than the mean preoperative value of each respective Ig class. Modified inotrope score was used to reflect frequent use of arginine vasopressin[9]; milrinone was not included in the inotrope score calculation because of ubiquitous use.

Intraoperative and Postoperative Management

A dose of 10 mg/kg methylprednisolone was given at 8 and 1 hour before transfer to the operating room (OR); no intraoperative steroids were given. The CPB circuit was primed with 25% albumin, mannitol, sodium bicarbonate, and Normosol-R (Hospira Inc, Lake Forest, Ill). Fresh frozen plasma (FFP; 20 mL/kg) was added to the prime for patients weighing less than 5 kg. Packed red blood cells (PRBCs) were added to the CPB circuit to maintain the desired hematocrit based on physiologic characteristics. All patients received zero-balance ultrafiltration during CPB and single-pass ultrafiltration after CPB. Del Nido cardioplegia was used for aortic crossclamping. Postoperative management was protocolized to target age- and physiology-specific hemodynamic and respiratory goals via inotrope titration, colloid boluses, and ventilator adjustments, as described elsewhere.[10] We followed a fluid-restrictive protocol including 25% maintenance intravenous fluids during the first 24 hours and maximally concentrated infusions. Starting on postoperative day (POD) 1, oncotic pressure was maintained with 25% albumin (1 g/kg) to keep serum albumin at 3 g/dL or higher. Starting in January 2011, all complex neonatal repairs received prophylactic PD within 6 hours of admission to the cardiac intensive care unit (CICU) (median, 2.5 hours); all other patients began to receive furosemide infusions on POD 1 and received passive peritoneal drainage.

Statistical Analysis

SPSS, version 21 (IBM, Chicago, Ill), was used for all statistical analysis. Continuous variables not normally distributed were summarized as a median with interquartile range, with a group comparison performed using the Wilcoxon rank sum test. Continuous variables with a normal distribution were summarized as means with SDs and compared using the unpaired Student *t*-test. Trends of immunoglobulin classes through time were compared with paired *t*-test. Categorical data were compared using the Fisher exact test. The Spearman rank correlation was used to determine the relationship between FFP transfusion and post-CPB Ig levels. $P \leq .05$ was considered statistically significant. All statistical tests were 2-tailed. Because the minimum detectable IgA and IgM levels reported by our clinical laboratory are 7 and 4 mg/dL, respectively, we substituted all values of IgA "<7 mg/dL" with 6 mg/dL (5 occurrences) and all values of IgM "<4 mg/dL" with 3 mg/dL (33 occurrences) for statistical analysis.

RESULTS

There were 150 stored plasma Ig results from the first 48 hours and 22 additional results beyond 48 hours; each sample analysis included IgA, IgG, and IgM. As a result of random depletion from the previous study, 38 time points had inadequate quantities of stored plasma available for Ig analysis; these were well balanced among study groups and time points. Sample contribution from each time point can be seen in Table 1. A total of 30 subjects had complete data, 16 of whom had hypogammaglobulinemia and 14 of whom had normal IgG at all time points. The median age and weight were 7 days and 3.2 kg, respectively. Other demographic data are presented in Table 2.

Immunoglobulin Concentrations

Table 1 shows mean and median Ig concentrations through the first 48 hours after CICU admission. There were 25 patients (53%) who had low post-CPB IgG (<248 mg/dL). In the 30 subjects for whom complete analysis of the initial 48 hours was possible, there was a 57% reduction (95% confidence interval, 45%-69%) in preoperative IgG levels at 24 hours and a 64% reduction (95% confidence interval, 52%-76%) at 48 hours (Figure 1). IgG remained lower than preoperative values for up to 7 postoperative days. For the 22 samples drawn for clinical purposes beyond 48 hours, the mean IgG concentration on POD 3 was 243 mg/dL (n = 7); POD 4, 236 mg/dL (n = 4); POD 5, 236 mg/dL (n = 3); POD 6, 270 mg/dL (n = 5); and POD 7, 221 mg/dL (n = 3). Both IgM and IgA levels were higher immediately after CPB and trended toward preoperative values over time (Figure 1). Five patients had low IgA and 4 patients had low IgM at some point post-CPB; all of these patients had

TABLE 1. Mean and median plasma immunoglobulin levels (mg/dL) over time

Sample time	IgG level	IgA level	IgM level
Pre-CPB (n = 32)			
Mean (95% CI)	604 (248-960)	10 (0-38)	17 (1-33)
Median (IQR)	585 (463-767)	6 (6-7)	16 (10-24)
Post-CPB (n = 41)			
Mean (95% CI)	490 (180-800)	85 (19-151)	59 (0-201)
Median (IQR)	512 (398-619)	81 (68-107)	44 (34-60)
24 h (n = 39)			
Mean (95% CI)	275 (51-499)	41 (9-73)	33 (0-103)
Median (IQR)	278 (193-349)	38 (32-54)	28 (18-34)
48 h (n = 38)			
Mean (95% CI)	330 (0-958)	27 (0-61)	23 (1-45)
Median (IQR)	229 (169-441)	24 (16-36)	21 (14-27)

Ig, Immunoglobulin; *CPB*, cardiopulmonary bypass; *CI*, confidence interval; *IQR*, interquartile range.

concomitant low IgG (data not shown). The first post-CPB IgA and IgM levels were strongly correlated with volume of FFP exposure in the OR ($r = 0.81$ and 0.84, respectively; $P < .001$), whereas IgG was not ($r = 0.29$, $P = .12$).

Clinical Outcomes

Table 3 shows a univariate comparison of demographics and clinical outcomes between patients with normal and low IgG. The mean IgG concentration at 48 hours in the low IgG group was 154 ± 61 versus 467 ± 282 mg/dL in those without hypogammaglobulinemia ($P < .0001$). Patients undergoing the Norwood and arterial switch operations and non-neonates were balanced between groups. Despite similar patient characteristics and risk factors, low IgG was associated with longer duration of mechanical ventilation, longer CICU stay, and a trend toward increased incidence of culture-proven infection. Only 3 patients (14%) with normal IgG acquired infections (1, *Pseudomonas* and *Enterobacter* ventilator-associated pneumonia [VAP]; 2, *Staphylococcus* bloodstream infection [BSI]; and 3, *Enterococcus* mediastinitis), whereas 10 patients (40%) in the low IgG group had infections (1, *Staphylococcus* BSI; 2, *Pseudomonas* BSI; 3, *Candida* in urine, *Candida* VAP, and *Bacillus* BSI [died of sepsis]; 4, *Pseudomonas* VAP; 5, *Enterococcus* BSI and mediastinitis; 6, *Staphylococcus* BSI; 7, *Candida* BSI [died of sepsis]; 8, *Staphylococcus* mediastinitis; 9, *Candida* VAP; and 10, *Enterobacter* VAP).

TABLE 2. Demographic variables (n = 47)

Variable	Value
Weight, kg	3.2 (2.9-3.6)
Age, d	7 (5-23)
Male sex	32 (68)
Diagnosis	
Hypoplastic left heart syndrome	21 (45)
Transposition of the great arteries ± VSD	15 (32)
Total anomalous pulmonary venous return	3 (6)
Tetralogy of Fallot	2 (4)
Atrioventricular septal defect	2 (4)
Interrupted aortic arch	4 (9)

All data are presented as median (interquartile range) or number (percentage). *VSD*, Ventricular septal defect.

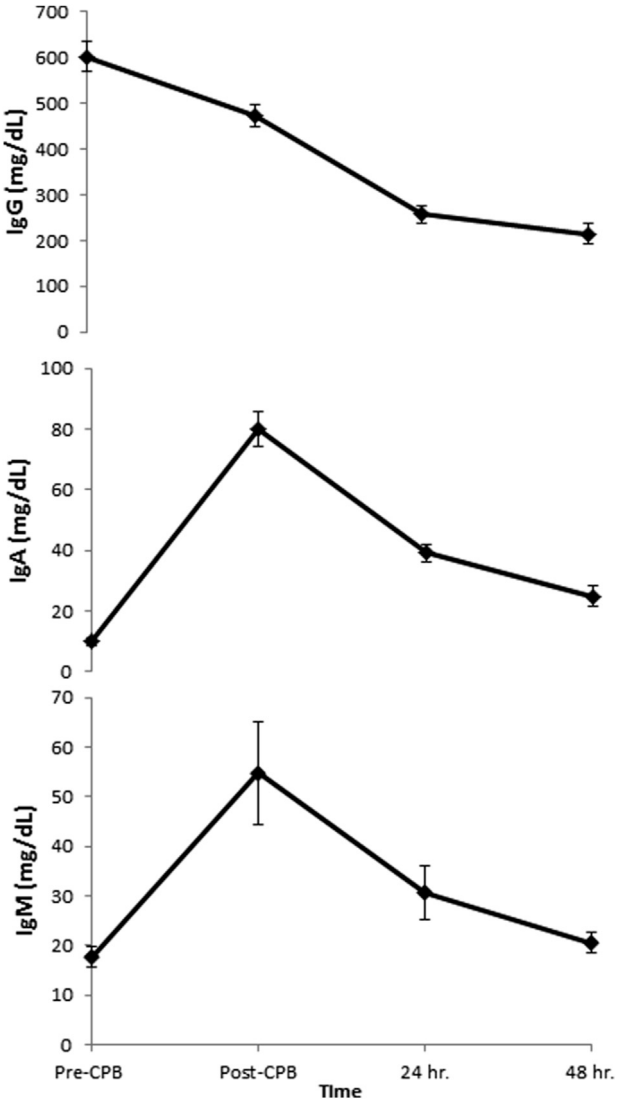

FIGURE 1. Plasma concentrations of immunoglobulin (*Ig*) G, IgA, and IgM over time. Data are given as mean with SEM (N = 30 for all time points). *CPB*, Cardiopulmonary bypass; *hr.*, hour.

Fluid Balance and Inflammation

Table 4 compares 24- with 48-hour fluid balance and protein concentration between the low and normal IgG groups. The low IgG group had more fluid resuscitation in the first 24 hours and significantly more positive net fluid balance at 24 and 48 hours. Although both groups had hypoalbuminemia and hypoproteinemia, the low IgG group

TABLE 3. Demographic, laboratory, and outcome variables compared between patients with low and normal immunoglobulin G after cardiopulmonary bypass

Variable	Normal IgG (n = 22)	Low IgG (n = 25)	*P* value
Median (IQR) age, d	6 (5-14)	10 (6-80)	.11
Cardiopulmonary bypass time, min	168 ± 58	180 ± 34	.40
RACHS-1 category	4.6 ± 1.1	4.6 ± 1.2	.82
Received 25% albumin on POD 1 to 2	7 (32)	11 (44)	.55
Postoperative peritoneal dialysis, No. (%)	9 (41)	11 (44)	1.0
White blood cell count, 10^9/L	13.1 ± 6.5	12.3 ± 4.3	.6
Absolute lymphocyte count, 10^9/L	1.86 ± 1.06	1.64 ± 1.23	.5
Hematocrit at 24 h, %	42 ± 7	43 ± 10	.48
Maximum serum creatinine, mg/dL	0.7 ± 0.2	0.9 ± 0.5	.01
Maximum lactate, mmol/L	6.5 ± 3.1	8.7 ± 5.1	.08
Maximum inotrope score	14.5 ± 5	16.8 ± 5.3	.13
Median (IQR) duration of ventilation, h	69 (38-100)	158 (91-296)	.013
Length of CICU stay, d	7 ± 3	16 ± 11	.001
Culture-proven infection, No. (%)	3 (14)	10 (40)	.056
Mortality, No. (%)	1 (4.5)	3 (12)	.61

Data are given as mean ± SD, except where indicated. The normal range of IgG represents the 95% confidence interval of preoperative average for all patients (248-970 mg/dL). Low IgG represents patients who had an IgG level 2 SDs lower than the mean at any point. *Ig*, Immunoglobulin; *IQR*, interquartile range; *RACHS*, Risk Adjustment for Congenital Heart Surgery; *POD*, postoperative day; *CICU*, cardiac intensive care unit.

TABLE 4. Fluid balance and related variables compared between patients with low and normal immunoglobulin G after cardiopulmonary bypass

Variable	Normal IgG (n = 22)	Low IgG (n = 25)	*P* value
First 24-h intake, mL/kg	159 (136-226)	225 (175-294)	.02
First 24-h output, mL/kg	207 (160-228)	212 (179-270)	.30
Chest tube output	54 (41-73)	63 (41-73)	.26
Urine output	39 (33-57)	36 (15-49)	.25
Peritoneal drain	106 (80-124)	97 (64-125)	.42
24-h Net fluid balance, mL/kg	−39 (−49 to 5)	11 (−28 to 46)	.02
48-h Net fluid balance, mL/kg	−118 (−154 to −55)	−53 (−100 to −29)	.01
FFP in CVOR, mL/kg	28 (14-59)	26 (16-49)	.94
FFP for first 24 h in CICU, mL/kg	13 (0-35)	10 (2-28)	.90
PRBCs in CVOR, mL/kg	13 (0-79)	16 (3-54)	.92
PRBCs for first 24 h in CICU, mL/kg	15 (0-32)	13 (2-28)	.94
Albumin, g/dL	3.1 ± 0.3	2.8 ± 0.3	.003
Total protein, g/dL	4.6 ± 0.4	4.1 ± 0.3	<.001

All data are presented as median (interquartile range) or mean ± SD. *Ig*, Immunoglobulin; *FFP*, fresh frozen plasma; *CVOR*, cardiovascular operating room; *CICU*, cardiac intensive care unit; *PRBC*, packed red blood cell.

had statistically significantly lower serum albumin and total protein than the normal IgG group. There was a similar incidence of 25% albumin replacement between groups. There was no difference in volume of FFP or PRBC transfusion between groups in either the OR or CICU. As demonstrated in Figure E1, patients who received PD were not more likely to have hypogammaglobulinemia after CPB. Pre-CPB cytokine levels were similar between groups, but the proinflammatory cytokines IL-6, IL-8, and IL-12 were significantly higher in the low IgG group post-CPB (Table E1).

DISCUSSION

To our knowledge, this is the first study describing the incidence of hypogammaglobulinemia in neonates after CPB. The results agree with previous adult and pediatric studies showing an immediate reduction in IgG that may be sustained several days post-CPB.[1,8,11] More important, this is the first pediatric study to show that acquired hypogammaglobulinemia after cardiac surgery may be associated with adverse clinical outcomes, including fluid overload, longer duration of mechanical ventilation, longer CICU length of stay, and increased risk of secondary infection. In addition, we show that preoperative Ig levels for neonatal patients with congenital heart disease are similar to those of healthy neonates.[12]

The specific mechanism of hypogammaglobulinemia after CPB in this population remains unclear. Some authors have attributed these changes to hemodilution during CPB.[3] We found a significant association between low IgG and hypoalbuminemia with 24- and 48-hour net-positive fluid balance, supporting this theory. The rate of decline after CPB is similar between all 3 Ig subclasses, as would be predicted from hemodilution of each (Figure 1). However, the fact that Ig concentration continues to decrease from 24 to 48 hours during a period of significant hemoconcentration (mean net fluid balance, −50 mL/kg) via diuresis and/or PD ultrafiltration suggests hemodilution alone cannot account for our findings. Potential sources of ongoing IgG losses include extravasation into the interstitial compartment because of increased capillary permeability and/or losses in urine, pleural fluid, or peritoneal fluid.

We provide indirect evidence that systemic inflammatory response syndrome (SIRS) may contribute to hypogammaglobulinemia via capillary leak of IgG into the interstitium and SIRS-associated volume resuscitation requirements (hemodilution). Neonatal CPB is associated with increased plasma concentration of proinflammatory cytokines, which have correlated with deleterious clinical outcomes.[13,14] Patients with a low IgG had increased

plasma concentrations of the proinflammatory cytokines IL-6, IL-8 and IL-12; hypoalbuminemia; and increased fluid overload consistent with SIRS.[15] During SIRS, IgG and other proteins, including albumin, leave the intravascular space and are lost in the interstitium.[2,16] A sustained reduction in plasma IgG may be the result of capillary leak of IgG into the pleural or peritoneal space, leading to IgG losses via surgical tube drainage. Although patients in our study did not have differences in 24-hour output (including chest tube output and peritoneal drainage), it is conceivable that the low IgG group had a higher concentration of IgG in these fluids because of increased capillary permeability to proteins. This possibility warrants further investigation.

The Ig measurements in this study came from banked plasma stored during a clinical trial evaluating the impact of PD after complex cardiac surgery.[17] Patients in this previous study had a peritoneal drain that was either used for PD (initiated at a median 2.5 hours after CICU admission) or left to passive peritoneal drainage. Although Katz and colleagues[18] showed that chronic PD in children is associated with hypogammaglobulinemia, our population did not demonstrate any difference in IgG concentration in patients who received early PD compared with those who did not. It is possible that IgG present in the peritoneal fluid is lost if the peritoneal drain is either used for dialysis or left to passive drainage and that hypogammaglobulinemia can occur in both situations.[4] The incidences of PD and total PD drainage were not different between groups in the first 24 hours (Table 4), and the precipitous post-CPB decline of IgG occurred before significant PD drainage (data not shown), suggesting that PD drains are not the major initial cause for post-CPB hypogammaglobulinemia. This remains speculative, however, because Ig levels were not measured in the peritoneal fluid.

There is a high incidence of acute kidney injury (AKI) after neonatal CPB.[19] Urinary filtration of Ig has been reported in other forms of kidney injury,[20] and patients with low IgG had significantly higher serum creatinine at 48 hours. It is unclear whether worse AKI played a causative role in increasing Ig losses or was merely a comorbid marker of increased severity of illness, along with hypogammaglobulinemia. There was no difference in 24-hour urine output between the 2 groups, making it less likely that urinary losses account for the difference in IgG concentration between groups. Ig concentration was not measured in the urine to evaluate this potential cause of hypogammaglobulinemia.

In contrast to IgG, both IgA and IgM increased after CPB. Interestingly, our review of the literature showed that there is no typical reaction of IgA or IgM levels to CPB. Studies have demonstrated that serum concentrations of IgA and IgM may decrease, increase, or not change after cardiac surgery.[1,3,8] In our patients, the immediate postoperative increase in IgM and IgA is likely a result of FFP transfusion. On average, all received 20 mL/kg FFP in the CPB prime and an additional nearly 30 mL/kg after CPB in the OR; those who received more FFP tended to have higher IgM and IgA concentrations. Acunas and colleagues[21] previously demonstrated that FFP transfusion in neonates with systemic inflammation increases IgM and IgA (but not IgG) levels at 24 hours. After the initial increase in IgM and IgA from FFP exposure, all 3 Ig classes decrease at the same rate, likely as a result of uniform exposure to some combination of hemodilution and capillary leak (Figure 1). Large molecules, such as IgM (900 kDa), are prone to extravasation during capillary leak, similar to smaller proteins, such as albumin (67 kDa) and IgG (150 kDa).[2] Because there were only a few patients who had low IgM or IgA, and all had concomitant low IgG, we did not attempt to determine if either was associated with increased morbidity.

Despite having similar risk factors, including age, weight, CPB time, and surgical complexity, patients with a low IgG had significantly worse clinical outcomes, including a trend toward increased incidence of secondary infection, more positive net fluid balance, and longer duration of mechanical ventilation and CICU length of stay. Postoperative secondary infection is a leading cause of morbidity and mortality after pediatric cardiac surgery (incidence, 13%-33%).[22] Pediatric cardiac surgical patients are vulnerable to infections due to systemic inflammation, blood product exposure, and multiple invasive medical devices. Although increased infections in the low IgG group may simply be due to the additive risk of multiple comorbid conditions and prolonged CICU length of stay, hypogammaglobulinemia may directly contribute. IgG plays an important role in the prevention of bacterial infections, and its deficiency is a known risk factor for infection in other pediatric populations.[6,7] IgG is an essential component of the humoral immune system; it helps activate the complement and phagocytic systems to fight pathogens. Neonates do not adequately produce IgG until approximately 3 months, relying instead on the long half-life of maternal IgG to protect them until that time.[23,24] Because of this limited synthesis and overall immaturity of the neonatal immune system, loss of IgG in neonates during the perioperative period may put them at increased risk for infection.

We often treat hypogammaglobulinemia with IVIG in our post-CPB pediatric patients. Some trials evaluating the impact of IVIG on clinical outcomes in critically ill patients have suggested a mortality benefit, but the limited studies evaluating its effect in post-CPB adult patients are mixed.[25-29] It is plausible that the low IgG group experienced increased infections at least in part because of their relative hypogammaglobulinemia. Two patients in the low IgG group died from sepsis. Whether

IVIG can prevent infections in patients with CPB-induced hypogammaglobulinemia is beyond the scope of this study to determine, but warrants further prospective investigation. If such studies are undertaken, it would be important to ascertain the appropriate IgG level threshold for treatment and optimal serum IgG level to target after administration of IVIG.

Limitations of our present study include its single-center retrospective design, which precludes making inferences about causality with respect to clinical outcomes and applicability to other centers. It is possible that protocols or procedures specific to our center led to increased (or decreased) incidence of hypogammaglobulinemia (ie, ubiquitous use of PD catheters). We did not analyze urine, chest tube output, or PD fluid for the presence of Ig; thus, we cannot rule any of them in or out as significant sources of Ig loss. All patients in this study received transfusions of FFP (which contains all Ig isotypes) in the OR, potentially increasing plasma Ig concentration immediately post-CPB,[21] although FFP and PRBC transfusion was uniform between groups. The overall infection rate in our cohort (27.6%) is in the higher range of what is reported after pediatric cardiac surgery, likely because of the high proportion of complex neonatal repairs (>80%) compared with other available studies. The infection rate in this high-risk population is likely high,[30] but has not been well defined. Our infection rate may limit the applicability of our findings to centers with lower infection rates. Four non-neonates were included in this data analysis (2 in each group); although not obvious from the data, it is possible their relatively more mature immune systems would lead to a different Ig response to CPB. In addition, some patients may have had an unknown immune deficiency, which could affect the results. Last, because the quantity of plasma in banked samples was not uniform, there were missing time points for some samples. Despite the fact that missing samples were random and well balanced between the 2 groups and among the time points, we cannot ensure these missing data would not have affected the results.

CONCLUSIONS

Hypogammaglobulinemia develops in more than half of neonates and infants after CPB, and may persist for up to 7 days. Post-CPB hypogammaglobulinemia is associated with increased inflammatory cytokines and morbidity, including increased positive fluid balance, CICU length of stay, duration of mechanical ventilation, incidence of AKI, and secondary infections. Prospective, randomized studies are needed to determine whether post-CPB hypogammaglobulinemia is a modifiable risk factor for unfavorable outcomes through treatment with IVIG.

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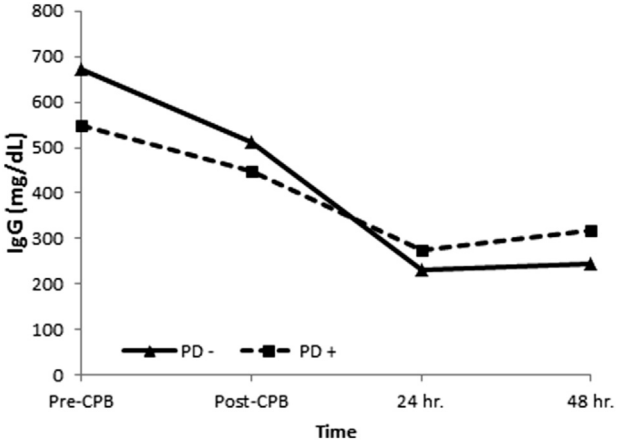

FIGURE E1. A comparison of mean plasma immunoglobulin (*Ig*) concentration over time between patients who received peritoneal dialysis within 6 hours after cardiopulmonary bypass (PD^+) and patients who did not receive peritoneal dialysis (PD^-). There was no statistical difference between PD^+ and PD^- patients at any time point. *CPB*, Cardiopulmonary bypass; *hr.*, hour.

TABLE E1. Comparison of plasma cytokine levels (pg/mL) between low and normal immunoglobulin G groups before and immediately after cardiopulmonary bypass

Cytokine	Normal IgG	Low IgG	*P* value
IL-1β			
Pre-CPB	0.46 (0.46-0.66)	0.5 (0.46-0.72)	.53
Post-CPB	0.74 (0.46-1.2)	1.1 (0.75-1.5)	.066
IL-6			
Pre-CPB	3.9 (1.5-6.6)	3.8 (1.2-11.4)	.83
Post-CPB	44.9 (27.1-60.8)	73.7 (37.9-125)	.037
IL-8			
Pre-CPB	13.5 (9.1-19)	14.5 (9.2-35)	.46
Post-CPB	117 (49.5-183)	187 (115.9-600)	.022
IL-10			
Pre-CPB	7.1 (3.9-10.1)	11.6 (5.2-18)	.09
Post-CPB	73.6 (28.5-156)	82 (45.7-257)	.185
IL-12			
Pre-CPB	0.78 (0.78-0.8)	1 (0.78-1.6)	.03
Post-CPB	2.8 (1.9-4.8)	6.3 (3.1-11.6)	.01
TNF-α			
Pre-CPB	4.9 (4-8.5)	6.1 (4.6-8.0)	.44
Post-CPB	7.6 (6.4-13.3)	13.7 (8.2-16)	.071

All values are presented as median (interquartile range). *Ig*, Immunoglobulin; *IL*, interleukin; *CPB*, cardiopulmonary bypass; *TNF*, tumor necrosis factor.